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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,571	12/31/2001	Etsuro Ogata	04853.0086	7887

22852 7590 05/18/2004

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,571	OGATA ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- *Failure to reply within the set or extended period for reply will, by statute, cause the application to become* ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *4-8,12,13,18,23 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-11,14-17,19-22 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/31/2001, 03/26/2002, 03/14/2003, 09/04/2003.*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In the previous office action mailed on May 4, 2004, the Examiner overlooked claims 21-25. Therefore, the office action mailed on May 4, 2004 is thereby vacated and replaced by the following new office action.

Election/Restrictions

2. Applicants' election with traverse of the following species on February 17, 2004 is acknowledged: *a substance that binds to a ligand of a PTH receptor/PTHrP receptor to inhibit binding between the ligand and the receptor from species* (i); *a disease mediated by PTH-or PTHrP-cytokine cascade* as listed in claim 11 from species (ii); and *IL-6* listed in claim 10 from species (iii). The traversal is on the ground(s) that this application was filed pursuant to 35 U.S.C. §371, restriction under 35 U.S.C. §121 does not apply to this application and the PCT unity of invention regulation do not contain a provision for the election of species.

This is not found persuasive because (i) restriction is required under 35 U.S.C. 121 and 372 for 35 U.S.C. §371 applications (see ¶ 18.19 of page 1875.02 of MPEP); (ii) PCT unity of invention regulations do contain a provision for the election of species under PCT Rule 13.2 (see ¶ 18.18 of page 1875.02 of MPEP).

In addition, Applicants submit that not all the PTH-or PTHrP-related disease, listed by the Examiner in species, are necessarily mediated by a PTH- or PTHrP-cytokine cascade. It is not appropriate to require that a species of cytokine from

species (iii) be elected. The Examiner wishes to clarify that if applicants elect a disease mediated by PTH-or PTHrP-cytokine cascade as listed in claim 11 from species (ii), Applicants are required to further elect a species of cytokine from species (iii), as Applicants have done so.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-25 are pending. Claims 1-3, 9-11, 14-17, 19-22, and 25 are under consideration. Claims 4-8, 12, 13, 18, 23, and 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Applicants' Amendment

4. Applicants' preliminary amendment, filed upon March 26, 2002 has been entered. Applicants' supplemental preliminary amendment, filed upon November 22, 2002 has also been entered. Claims 1-20 have been amended. New claims 21-25 have been added.

Priority

5. Acknowledgment is made of applicant's claim for foreign priority based on an application, JAPAN 11/189793, filed in Japan on July 2, 1999. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

6. The information disclosure statements filed on 12/31/2001, 03/26/2002, 03/14/2003, and 09/04/2003 have been considered by the Examiner and a signed copy of the substitute form PTO-1449 is attached to the office action.

Drawings

7. The drawings filed on 12/31/2001 are accepted by the Examiner.

Objection to the Disclosure

8. The disclosure is objected to because of the following informalities:

(i) The brief description of drawings fails to refer to panels A-D of Fig. 4 and panels A and B of Fig. 5.

(ii) The incorporation of essential material (information regarding a PTH/PTHrP type I receptor) in the specification by reference to a foreign patent application is improper (2nd paragraph of page 7 of the instant specification). Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d

579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Appropriate correction is required.

Claim Rejections—35 USC § 112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3, 9-11, 14-17, 19, 20-22, and 25 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method of treating PTHrP-relatd hypercalcemia, septicemia, and cachexia with an anti-PTHrP antibody, does not reasonably provide enablement for (i) a method of treating any other PTH/PTHrP related diseases with an anti-PTHrP antibody; (ii) a method of treating a PTH/PTHrP related disease with any other substance that binds a ligand of PTH receptor or PTHrP receptor; and (iii) a method of preventing a disease mediated by PTH/PTHrP with a substance that binds a ligand of PTH/PTHrP receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of

working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claim. In view of Applicants' species election, claim 1 recites a method of treating or preventing a disease mediated by PTH or PTHrP comprising administering to a patient at least a substance that binds to a ligand of PTH receptor or PTHrP receptor to inhibit the binding between the ligand and receptor. All other claims depend from claim 1, either directly or indirectly. Thus, the claims are broad and encompass a method of treating or even preventing any PTH/PTHrP mediated diseases with any substances that bind to any ligands of any PTH receptors or PTHrP receptors.

Nature of the invention and the state of the prior art. The present invention is related to a method of treatment for diseases caused by parathyroid hormone (PTH) or parathyroid hormone-related protein (PTHrP). PTHrP shares N-terminal sequence homology with PTH, so that both peptide activates a common G protein-linked receptor termed the PTH/PTHrP type I receptor. PTH produced in the parathyroid gland regulates calcium and phosphorous metabolism by activating the PTH/PTHrP receptor in bone and kidney. The ability of PTHrP to activate the PTH/PTHrP type I receptor in these tissues accounts for its hypercalcemic actions in patients with pathological overexpression of the peptide due to unregulated production by cancer cells (see, e.g., Qian et al., Endocrinology, 140: 1826-1833,

1999). However, another member of the PTH/PTHrP receptor family has also been identified and its natural ligand has been identified as tuberoinfundibular peptide 39. The PTH type 2 receptor is only activated by PTH, but not by PTHrP (see, e.g., Qian et al., Endocrinology, 140: 1826-1833, 1999).

The prior art teaches treatment of PTHrP-related hypercalcemia, septicemia, and cachexia with an PTHrP antagonist, including an anti-PTHrP antibody (Sato et al. US2002/0165363 A1, Publication Date: November 7, 2002; Grunfeld et al., WO 96/39184, December 12, 1996; Grunfield et al., U.S. Patent No. 5,660,826, August 26, 1997; Sato et al., JAPAN 11080025, March 23, 1999). However, there is no treatment that is known in the art to prevent any diseases mediated by PTH/PTHrP. The prior art does not teach a method of treating any PTH/PTHrP related diseases other than hypercalcemia, septicemia, and cachexia with an anti-PTHrP antibody or a method of treating a PTH/PTHrP related disease with any substance that binds a ligand of PTH receptor or PTHrP receptor other than an anti-PTHrP antibody.

The amount of direction or guidance presented and the existence of working examples. While providing sufficient directions and working examples on how to make an anti-PTH or anti-PTHrP antibody and treat PTHrP related diseases, hypercalcemia, septicemia, and cachexia with an anti-PTHrP antibody, the specification fails to provide sufficient guidance, directions or working examples on (i) how to treat any other diseases with an anti-PTHrP antibody; (ii) how to make and use any other substance that binds to a ligand of the PTH/PTHrP receptor; (iii) how to prevent a disease mediated by PTH/PTHrP with a substance that binds a ligand of

the PTH/PTHrP receptor. There are no sufficient directions regarding whether an anti-PTH antibody acts as effectively as an anti-PTHrP antibody in the method of treating any diseases.

Furthermore, claim 14 recites a PTH/PTHrP type I receptor. Cearly, the structure of the receptor is essential to practice the claimed invention. Without the information on the structure of the receptor, one cannot practice the claimed invention. However, such essential material in the specification is merely referred to a foreign patent application (2nd paragraph of page 7). It is noted that such essential material cannot be incorporated by references other than to issued U. S. patents or U.S. patent applications to be issued. See, MPEP §608.01(p)(page 600-79).

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary. Although one skilled in the art can certainly make and use the anti-PHTrP antibody to treat hypercalcemia, septicemia, and cachexia, which are mediated by PTHrP (or PTHrP-cytokine cascade). An artisan would not be able to make any substance other than an anti-PTHrP/PTH antibody because the instant specification fails to disclose sufficient information on the structure, chemical, and physical property of the genus of "substance". It is unpredictable whether such an anti-PTHrP antibody can be used in treatment of other diseases, such autoimmune disease which is listed as a disease mediated by PTH- or PTHrP-cytokine cascade (see claims 9-11), or a central nervous system disease mediated by PTH or PTHrP because each disease has its unique pathological conditions. It is also unpredictable whether an anti-PTHrP

antibody and an anti-PTH antibody will have the similar efficacy in treating a given disease. In this respect, it is noted that there are at least two different receptors in the PTH/PTHrP receptor family that shows different binding affinities for PTH or PTHrP, as discussed above. Thus, treatment of a disease related to PTHrP, for example, cachexia, septicemia or hypercalcemia, with an anti-PTH antibody is unlikely to be successful because such a disease is mediated by PTHrP and inhibition of binding of PTH to its receptor (e.g., either a type I receptor or a type II receptor) would not necessarily inhibit binding of PTHrP to its receptor. Thus, without sufficient directions, undue experimentation would have to be done before one skilled in the art can practice the claimed method.

Accordingly, while being enabling for a method of treating PTHrP-relatd hypercalcemia, septicemia, and cachexia with an anti-PTHrP antibody, does not reasonably provide enablement for (i) a method of treating any other PTH/PTHrP related diseases with an anti-PTHrP antibody; (ii) a method of treating a PTH/PTHrP related disease with any substance that binds a ligand of PTH receptor or PTHrP receptor other than anti-PTHrP antibody; and (iii) a method of preventing a disease mediated by PTH/PTHrP by a substance that binds a ligand of the PTH/PTHrP receptor. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

11. Claims 1-3, 9-11, 14, 19, 21, and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claim 1 recites a method of treating or preventing a disease mediated by PTH or PTHrP comprising administering to a patient at least *a substance* that binds to *a ligand* of PTH receptor or PTHrP receptor to inhibit the binding between the ligand and receptor. Claims 2, 3, 9-11, 14, 19, 21, and 25 depend from claim 1, either directly or indirectly. The claims do not require that the "substance" possess any particular conserved structure or disclosed distinguishing feature.

However, other than an anti-PTH antibody or an anti-PTHrP antibody, the instant specification does not provide sufficient description for the substance that binds to a ligand of PTH receptor or PTHrP receptor. The specification refers "a substance binding to a ligand of PTH receptor or PTHrP receptor to inhibit binding between the ligand and the receptor" as a substance (e.g., an anti-PTH antibody, an anti-PTHrP antibody, etc.) which inhibits binding of a ligand (e.g., PTH, or PTHrP etc) to a PTH receptor or PTHrP receptor by binding to the ligand of PTH receptor or PTHrP receptor" (3rd paragraph of page 8 of specification); the specification refers "a

ligand" as a substance binding to an enzyme receptor (2nd paragraph of page 8 of specification). Since the two terms encompass compounds with diversified structures, the specification fails to provide sufficient description information, such as definitive structural features of the genus of "substance" or "ligand". There is no description of the conserved regions that are critical to the structure and function of the genus claimed, or relation of the structure to the recited activity.

The specification also fails to provide a reasonable number of representative species of the genus. The instant disclosure only provides a limited number of examples without providing information on how the structure of disclosed ligand example is representative of other unknown ligands having the same binding activity to the receptor or how the structure of disclosed anti-PTH antibody or anti-PTH-RP antibody is representative of other unknown "substance" that binds a ligand of the PTH receptor or PTHrP receptor and thus inhibits the binding of the PTH/PTHrP receptor and its ligand. Furthermore, the prior art does not provide compensatory structural or correlative teachings for the claimed broad genus of the molecules. It is noted that only description of what a compound does without disclosure of the chemical structure of the compound, as is the case here, is not sufficient to satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

Due to the breadth of the claim genus and lack of the definitive structural of the claimed genus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus.

Claim Rejections—35 USC § 112, 2nd paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-3, 9-11, 14-17, 19-22, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "a ligand of either receptor" in part b). There is insufficient antecedent basis for this limitation in the claim.

Claim 3 is indefinite because it recited "QQL" which is an abbreviation for "quality of life" (the middle of page 8 of the specification). It is unclear what are the metes and bounds of the term are. The specification fails to unambiguously define the term, rendering the claim indefinite.

Claims 2, 9-11, 14-17, 19-22, and 25 are rejected as dependent claims from claim 1, either directly or indirectly.

Claim Rejections—35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in
>
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only

if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1-3, 9-11, 14-17, 19-22 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Sato et al. (US2002/0165363 A1, Publication Date: November 7, 2002; earliest priority date: May 15, 1997).

Sato et al. teach a therapeutic agent for cachexia, an anti-PTHrP antibody, including a humanized #23-57-137-1 antibody, which inhibits the binding of PTHrP to its receptor (see, e.g., claims 1-8). Treatment of cachexia with the humanized #23-57-137-1 anti-PTHrP antibody increased survival rate (Fig. 1) and reduced the loss of body weight in mice with cachexia (Fig. 3). The humanized #23-57-137-1 antibody, which is the same antibody disclosed in the instant application (see page 38 of the instant specification), inhibits the binding of PTHrP to PTHrP type 1 receptor. The cachexia, which is distinct disease from hypercalcemia and is listed in claim 11 as one of the diseases mediated by PTHrP-cytokine (IL-6), is necessarily mediated by a PTH/PTHrP type I receptor and reduces quality of life (QOL) of patients (e.g., loss of body weight; see the control group of Fig. 3). Thus, the reference of Sato et al. meets the limitations of claims 1-3, 9-11, 14-17, 19-22, and 25.

16. Claims 1-3, 9-11, 14-17, 19-22, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Grunfeld et al. (WO 96/39184, December 12, 1996).

Grunfeld et al. teach treatment of systematic inflammatory response syndrome, including septicemia (1st paragraph of page 1; line 2 of page 3), with an anti-PTHrP antibody (Abstract; lines 5-26 of page 1; claims 1, 6, and 7), which inhibits the binding of PTHrP to its receptor. The antibody includes monoclonal

antibodies or a humanized antibody (bottom of page 5). The anti-PTHrP antibody inhibits, by its nature, the binding of PTHrP to the PTHrP type 1 receptor. The septicemia, which is distinct disease from hypercalcemia and is listed in claim 11 as one of the diseases mediated by PTHrP-cytokine (IL-6), is necessarily mediated by a PTH/PTHrP type I receptor and reduces quality of life (QOL) of patients. Thus, the reference of Grunfeld et al. meets the limitations of claims 1-3, 9-11, 14-17, 19-22, and 25.

Claim Objections—Minor Informalities

17. Claims 1-3, 9-11, 14-17, 19-22, and 25 are objected to because of the following informalities: (i) claims 1-3, 9-11, 14-17, 19-22, and 25 recite non-elected subject matter (species); (ii) claims 14-17 and 20 depend, in part, on non-elected claims 4-8, 12, and 13, either directly or indirectly.

Appropriate correction is required.

Conclusion

18. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00

pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. The fax number for this Group is (703) 872-9306.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Ruixiang L.

Ruixiang Li, Ph.D.
Examiner
May 13, 2004